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Research Progress on Pathogenesis and Treatment of Cancer - related Fatigue

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Abstract

Cancer-related fatigue (CRF) is one of the most painful symptoms of cancer patients, and the specific pathogenesis of the disease is not known, and may be related to gene expression and signal transmission, skeletal muscle and mitochondrial abnormalities, inflammatory response and immune disorders, cancer itself and its treatment and others. Clinically, non-drug therapy is the main treatment, and traditional Chinese medicine (TCM) has a certain advantage in the treatment of CRF. This article will summarize the possible pathogenesis of CRF and the treatment of traditional Chinese and western medicine in recent years.

Keywords

Cancer-related Fatigue (CRF); Pathogenesis; Traditional Chinese and Western Medicine Treatment.

1. Introduction

The National Comprehensive Cancer Network (NCCN) defines it as a painful, persistent, subjective feeling of physical, emotional, or cognitive fatigue or exhaustion associated with cancer or cancer treatment that is disproportionate to recent activity and interferes with normal functioning. [1] CRF is more severe and painful than normal fatigue, and is not alleviated by sleep and rest, making it impossible for patients to participate in normal work and daily activities and seriously affecting quality of life. Fatigue usually worsens during cancer treatment, with 30 to 60 percent of patients reporting moderate to severe fatigue during treatment, so treatment is often interrupted. [2] At present, the exact pathogenesis of CRF is not clear, and there is a lack of effective treatment. This article reviews the pathogenesis of CRF and the treatment methods of Traditional Chinese and Western medicine, in order to provide reference for research and clinic.

2. Pathogenesis of cancer-related fatigue

2.1. Abnormal gene expression and signal transduction

In recent years, several studies have shown that genes play an important role in CRF. Sestrins is a stress-inducing gene with antioxidant properties, and SESN3 is a member of the Sestrin family of genes, and down regulation of SESN3 has been shown to be associated with increased fatigue during radiotherapy. [3] SESN3 may serve as an intervention target and biomarker for EBRT-related fatigue related cellular and molecular events. Disorders in a group of 35 genes have recently been shown to predict fatigue development in prostate cancer (PCP) patients undergoing radiation therapy. [4] Abnormal genes are involved in neural, immune, mitochondrial, muscular and metabolic pathways, ionizing radiation sensitivity, DNA damage and DNA repair frequency changes. Several genes have also been linked to depression and may

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emphasize variable radiosensitivity in patients prone to radiation-induced fatigue. Single nucleotide polymorphisms (SNPs) are one of the most common types of genetic variation in the human genome, and are the basis of differences in human susceptibility to diseases. A study involving 568 colorectal cancer patients to investigate the association between SERT gene promoter single nucleotide polymorphisms (SNPs) rs25531 and rs956304 and CRF in colorectal cancer showed that SERT gene promoter SNPrs25531 was associated with CRF in colorectal cancer patientsG genotype was an independent risk factor for CRF in colorectal cancer patients. [5] Specific polymorphisms of TNF-α, IL-1β, IL-4, and IL-6 genes were associated with increased fatigue, and a series of polymorphisms of HLA, IFN-γ, 5-HT, and NR3C1 genes were found in patients with CRF. However, these SNPS (excluding INF-γ) have not been adequately studied in CRF. [6] A validation of inflammatory gene variants associated with long-term CRF in a large breast cancer cohort suggests that individual SNPs are unlikely to have clinical use. [7] It has been reported that neurotransmitter genes play a role in the development and maintenance of fatigue and energy levels in cancer patients through a large number of neurotransmitters. [8]

A study exploring new genetic signals suggests that mGluR5 signaling on T cells may play a key role in the development of chronic inflammation, leading to fatigue, and leading to differences in individual immune responses to radiation. [9] CRF has been shown to be associated with increased activity of pro-inflammatory transcription factor NF-κB and decreased activity of the antiviral IRF transcription factor family. [10] Related apoptosis-inducing ligand (TRAIL) and TRAil-inducing receptor TNFRSF10C (TRAIL-R3) were significantly upregulated in fatigued TUMOR necrosis factor subjects, and TRAIL was associated with post-radiation fatigue score. [11] The influence of gene expression and signal transducment on CRF needs to be investigated more vigorously.

2.2. Abnormality of skeletal muscle and mitochondria

Skeletal muscle mass has been identified as a potential risk factor for fatigue treatment. Skeletal muscle metabolism changes, skeletal muscle atrophy, muscle contractility deficiency changes, and muscle electrophysiological abnormalities are all factors that contribute to muscle fatigue in cancer patients. Research suggests that skeletal muscles to reduce the incidence of patients with CRF and severity increased significantly, skeletal muscle decrease may be important targets to improve the treatment of CRF, and serum albumin and cholinesterase and skeletal muscle to reduce disease staging and CRF have statistical correlation, circulating albumin and cholinesterase can serve as biomarkers of predicted less muscle disease. [12] Mitochondria are cytoplasmic organelles involved in energy production, reactive oxygen species (ROS) production and apoptosis regulation. At the same time of inducing cell apoptosis, chemotherapy drugs can produce excessive ROS, which can destroy mitochondrial components and lead to mitochondrial dysfunction. Damage to the electron transport chain (ETC) responsible for the production of adenosine triphosphate (ATP) through oxidative phosphorylation may trigger more ROS production, leading to a vicious cycle that may lead to the development of CRF. Mitochondrial DNA (MtDNA) content is a biomarker of mitochondrial dysfunction, which can be measured in peripheral blood and has been shown to be associated with the development of CRF after chemotherapy. [13] It has been reported that after prostate cancer patients received local radiotherapy (XRT), mitochondria of mononuclear cells were defective in oxidation from complex III onwards. [14] Patients with prostate cancer experience fatigue symptoms during radiation therapy, and reduced oxidation of complex III appears to be associated with increased fatigue symptoms, and complex III may play a role in the formation of radiation-induced fatigue. Mitochondria are the main organelles of cells, providing 95% of the energy required by cells through oxidative phosphorylation, and playing an important role in the regulation of calcium

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signaling, apoptosis, immune signaling, and other intracellular signaling events. Therefore, mitochondrial abnormalities may lead to fatigue. [15]

2.3. Inflammatory response and immune disorders

CRF may be related to a variety of inflammatory factors and immune responses. Low levels of inflammation alter metabolic patterns, reduce metabolic efficiency, and lead to increased reactive oxygen species and insulin insensitivity. [16] These effects can lead to reduced energy supply to cells, which can lead to sustained fatigue.The cytokine IL-12 has been shown to be associated with fatigue before and after chemotherapy. [17] The fatigue degree of stage I and II breast cancer patients was proved to be different from the levels of IL-6 and TNF-α. [18] Immunological changes prior to CRF may reflect long-term responses to radiation-induced damage, such as IL-3, IL-8, IL-9, IL-10, IL-16, IP-10, IFN-α2, IFN-γ, and SDF1α. [19] INF-γ-inducible protein (IP-10), also known as CXCL-10, plays a role in lymphocyte infiltration at tumor sites, but IP-10's role as a biomarker of CRF remains uncertain. [20] Studies have shown that significant associations between IL-6 and angiogenesis related biomarkers (sicAM-1, VEGFD) and cancer-related fatigue were observed at several time points in patients with colorectal cancer. [21] Higher neuroticism score, obesity, and higher PAR index were significantly associated with increased risk of CRF, suggesting that low levels of immune activation and inflammation are the basis for CRF in lymphoma survivors. [22]

2.4. Caused by cancer-related treatment

CRF can be caused or aggravated by cancer-related treatments, such as radiation, chemotherapy, and surgery. Studies have shown that maximum radiation doses to the brainstem and medulla in patients with head and neck cancer are associated with a significantly increased risk of fatigue in acute patients. [23] Regorafenib (REG) is a novel oral polytyrosine kinase inhibitor that can be used in the treatment of progressive metastatic colorectal cancer. [24] REG rapidly causes hypothyroidism in about 50% of patients, and also triggers thyroid autoimmunity in a small number of patients. Studies have confirmed that reG-induced hypothyroidism is strictly related to fatigue. [25] Aromatase inhibitors (AIs) are the first-line adjuvant for postmenopausal endocrine therapy in hormone receptor-positive breast cancer patients, and more than 50% of aromatase inhibitor users report moderate to severe fatigue. [26] Oxidative stress is a state in which the production rate of reactive oxygen species exceeds the ability of cells to protect, adapt and repair, leading to damage to local tissues, including lipid membranes, protein structures and nucleic acids. [27] Oxidative stress may be related to CRF, and the increase in antioxidant capacity after exercise intervention may play a role in alleviating CRF in cancer survivors.

The significant correlation between fatigue changes and protein oxidation and antioxidant capacity suggests that systemic oxidative stress may be a potential mechanism of CRF.

2.5. Caused by the patient's own disease

CRF is not only linked to the cancer itself, but can also aggravate fatigue. Regardless of the patient's inflammation, the tumor causes fatigue. [28] The study found that cancer causes the body to be in a persistent stress state, causing endocrine function to decline and further fatigue. [29] Depression, anxiety and stress are associated with cancer and may lead to CRF by suppressing the immune system and inflammatory changes. [30,31] Nausea, sleep disturbance and younger age are significant risk factors for CRF after chemotherapy. [32] In cancer patients undergoing radiotherapy, youth, depressive symptoms, and androgen deprivation therapy have been associated with increased fatigue. [33] Progression phobia (FOP) is a common symptom in cancer patients, and FOP mediates the relationship between CRF and different aspects of quality of life. [34] HPV status and inflammation were found to be independent

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predictors of fatigue over time, with patients with HPV-related tumors experiencing a significant increase in fatigue during treatment. [35]

3. TCM treatment

3.1. Acupuncture and massage

Lijun et al. found that three-injection therapy for fatigue was an effective choice for the treatment of CRF, with the characteristics of definite and quick efficacy. [36,37] A meta-analysis of 1327 patients showed that acupuncture significantly reduced CRF, especially in breast cancer patients, compared with sham acupuncture or conventional treatment. [38] A randomized, double-blind, placebo-controlled preliminary trial suggested that acupuncture may be a safe and feasible adjunctive therapy in CRF palliative care. [39] Atefeh et al. selected acupuncture points Zusanli (ST36), Hegu (LI4) and Sanyinjiao (SP6) to carry out clinical experiments, which showed that acupressure had short-term effect on cancer-related fatigue in chemotherapy patients. [40]

3.2. Chinese herbal therapy

Guodong et al. demonstrated through animal experiments that Shen Qi injection could inhibit the dysfunction of exhausted T cells by inhibiting the pro-inflammatory cytokines produced by peripheral blood immune cells, and improve fatigue symptoms and anti-tumor immune function by targeting immune avoidance molecules PDL1, TIM3 and FOXP3. [41] Oral ginseng extract can significantly improve CRF with small side effects, but further studies are needed for the treatment of CRF. [42] A phase II randomized controlled trial showed that Renshen Yangrong decoction granule could significantly improve the fatigue degree and function of cancer patients. [43] Studies have shown that TCM treatment may promote liver glycogen synthesis, change intestinal microflora composition and reduce physical and mental fatigue caused by colorectal cancer by inhibiting inflammatory response. [44]

3.3. Tai Chi and Baduanjin

A meta-analysis of 373 patients showed that tai Chi over 8 weeks had a short-term improvement in CRF that was superior to physical exercise and psychological support, especially in breast and lung cancer patients. [45] Yun et al. confirmed that Baduanjin Qigong exercise can effectively relieve CRF and improve the level of physical activity and sleep quality of patients. [46]

4. Modern medicine (Western medicine) treatment

4.1. Drug therapy

A network pharmacological analysis based on an animal model experiment suggests that the active vitamin D metabolite 1,25 (OH)2D3 May improve CRF in tumor-bearing mice by altering the levels of inflammatory cytokines and the direction of tryptophan metabolism. [47] Sunitinib is a kind of tyrosine kinase inhibitors for the treatment of metastatic renal cell carcinoma, but will cause the CRF adverse effects, such as L-carnitine is a kind of associated with energy metabolism of amino acids, a single center prospective pilot study confirmed that l-carnitine supplementation can be improved by using chougny for his treatment of the CRF. [48] Chemotherapy can disrupt the balance of carnitine in cancer patients, and carnitine plays an important role in ATP synthesis. Carnitine deficiency is prone to the occurrence of CRF in patients, Kazuhira et al. [49] showed that carnitine supplementation can improve CRF. However, a meta-analysis of 12 studies found that the low risk of bias did not support the use of carnitine supplements for CRF. [50] Minocycline is a broad-spectrum tetracycline antibiotic, which can regulate nerve and inflammation. A phase II clinical trial confirmed that minocycline

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can reduce chemotherapy-related fatigue in patients with non-small cell cancer with low toxicity. [51] It can be used in phase III clinical trials. Administration of corticosteroids is one of the common options for relieving CRF. A clinical study of 105 cancer patients showed that dexamethasone was effective in reducing fatigue during treatment with REG, prolonging the duration of dose adjustment for REG, and reducing the incidence of anorexia and hand and foot skin reactions. [52] Yuko et al. found that the initial daily dose of betamethasone, the number of days from the start of medication to death, the number of days without fentanyl and advanced age were all factors affecting the efficacy of betamethasone. [53]

4.2. Non-drug therapy

Multimodal approach has certain advantages in treating chronic cancer-related fatigue. [54] A comprehensive cohort study of 126 breast cancer patients showed that multimode therapy (psychoeducation, fitness therapy, painting therapy, sleep education/restriction combined with aerobic exercise) was significantly better than aerobic exercise alone in improving CRF. [55] A longitudinal study of 68 children with cancer showed that increased physical activity was associated with reduced CFR. [56] A randomized controlled trial demonstrated that comprehensive experiential training programs and counselling were effective in promoting physical activity and reducing CRF in children with cancer, providing an alternative means to reduce the burden of health care. [57] William et al. demonstrated that risk-based training can effectively improve self-efficacy and quality of life, and improve fatigue symptoms in children with cancer. [58] Scott et al. found that high-intensity training (HIIT) significantly improved CRF and mental health-related quality of life (HRQoL) in cancer patients. [59] A randomized controlled trial of 240 patients [60] showed that HIIT was effective in preventing the increase of CRF during chemotherapy for breast cancer and alleviating the burden of symptoms in patients, and high intensity interval exercise should be targeted in the treatment of cancer patients. [60] Qi et al. demonstrated that nurse-led family exercise and behavioral cognitive therapy can reduce CRF and depression symptoms and improve sleep quality in ovarian cancer patients. [61] Favil et al. found that exercise during adRT seemed feasible and well tolerated to enhance body function while minimizing adverse changes in body composition and CRF. [62] Open-label placebo (OLP) has been shown to improve symptoms of certain diseases, and a randomized controlled trial of 40 cancer survivors confirmed that placebo also improved CRF in cancer survivors when administered open, possibly related to the dopaminergic system. [63] Eric et al. found that OLP may be a beneficial treatment for CRF, but replication studies are needed. [64] Jillian et al. randomly assigned 81 subjects to either a bright white light group (intervention group, n=42) or a weak red light group (control group, n=39), and the results supported the use of light therapy to improve fatigue symptoms in cancer patients. [65] Lisa et al. found that systematic morning exposure to bright light may have beneficial effects on sleep in tired cancer survivors. [66] A national multi-center phase III randomized controlled trial involving 410 cancer survivors demonstrated that yoga was effective in the treatment of CRF in cancer survivors, particularly improvements in sleep and daytime dysfunction. [67] Anna et al. found that yoga therapy can effectively improve anxiety, depression and fatigue symptoms of cancer patients. [68] Suzanna et al. demonstrated that a fatigue reduction diet (a diet rich in fruits, vegetables, whole grains, and omega-3 fatty acids) can be used as a safe and sustainable treatment to improve CRF compared to an attention control group (general health course). [69]

5. Summary

To sum up, the difficulty in the treatment of CRF lies in the unknown pathogenesis and the lack of comprehensive and unified evaluation tools, so targeted treatment cannot be given. CRF, as a concomitant symptom of cancer and its treatment, seriously affects the quality of life of patients. TCM treatment focuses on syndrome differentiation and treatment, which can not only

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solve the problem of unclear mechanism of CRF, but also has the characteristics of safety, effectiveness and small toxic and side effects. It has great research value and application prospect in the treatment of CRF.

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Yingchao Wu and Dajin Pi performed the data collection and wrote the manuscript. Yiliu Chen analyzed the data. Mingzi Ouyang provided the initial idea. All authors read and approved the final manuscript.

The authors declare that there is no conflict of interest regarding the publication of this paper.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Reference

[1] Berger AM, Mooney K, Alvarez-Perez A et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw. 2015;13(8):1012-39.

[2] Bower JE. The role of neuro-immune interactions in cancer-related fatigue: Biobehavioral risk factors and mechanisms. Cancer-Am Cancer Soc. 2019;125(3):353-364.

[3] Gonzalez VJ, Abbas-Aghababazadeh F, Fridley BL, Ghansah T, Saligan LN. Expression of Sestrin Genes in Radiotherapy for Prostate Cancer and Its Association With Fatigue: A Proof-of-Concept Study. Biol Res Nurs. 2018;20(2):218-226.

[4] Hashemi S, Fernandez MJ, Saligan L, Sonis S. Exploring Genetic Attributions Underlying Radiotherapy-Induced Fatigue in Prostate Cancer Patients. J Pain Symptom Manage. 2017;54(3):326-339.

[5] Ouyang X, Zhang G, Pan H, Huang J. Susceptibility and severity of cancer-related fatigue in colorectal cancer patients is associated with SLC6A4 gene single nucleotide polymorphism rs25531 A>G genotype. Eur J Oncol Nurs. 2018;33:97-101.

[6] Wang T, Yin J, Miller AH, Xiao C. A systematic review of the association between fatigue and genetic polymorphisms. Brain Behav Immun. 2017;62:230-244.

[7] Kuhl T, Behrens S, Jung AY et al. Validation of inflammatory genetic variants associated with long-term cancer related fatigue in a large breast cancer cohort. Brain Behav Immun. 2018;73:252-260.

[8] Eshragh J, Dhruva A, Paul SM et al. Associations Between Neurotransmitter Genes and Fatigue and Energy Levels in Women After Breast Cancer Surgery. J Pain Symptom Manage. 2017;53(1):67-84.e7.

[9] Feng LR, Fernandez-Martinez JL, Zaal K et al. mGluR5 mediates post-radiotherapy fatigue development in cancer patients. Transl Psychiatry. 2018;8(1):110.

[10] Xiao C, Beitler JJ, Higgins KA et al. Differential regulation of NF-kB and IRF target genes as they relate to fatigue in patients with head and neck cancer. Brain Behav Immun. 2018;74:291-295.

[11] Feng LR, Suy S, Collins SP, Saligan LN. The role of TRAIL in fatigue induced by repeated stress from radiotherapy. J Psychiatr Res. 2017;91:130-138.

[12] Wang B, Thapa S, Zhou T et al. Cancer-related fatigue and biochemical parameters among cancer patients with different stages of sarcopenia. Support Care Cancer. 2020;28(2):581-588.

ISSN: 2710-0588 DOI: 10.29556/FSE.202109_1(6).0022

[13] Chae JW, Chua PS, Ng T et al. Association of mitochondrial DNA content in peripheral blood with cancer-related fatigue and chemotherapy-related cognitive impairment in early-stage breast cancer patients: a prospective cohort study. Breast Cancer Res Treat. 2018;168(3):713-721.

[14] Hsiao CP, Chen MK, Daly B, Hoppel C. Integrated mitochondrial function and cancer-related fatigue in men with prostate cancer undergoing radiation therapy. Cancer Manag Res. 2018;10:6367-6377.

[15] Chae JW, Chua PS, Ng T et al. Association of mitochondrial DNA content in peripheral blood with cancer-related fatigue and chemotherapy-related cognitive impairment in early-stage breast cancer patients: a prospective cohort study. Breast Cancer Res Treat. 2018;168(3):713-721.

[16] Lacourt TE, Vichaya EG, Chiu GS, Dantzer R, Heijnen CJ. The High Costs of Low-Grade Inflammation: Persistent Fatigue as a Consequence of Reduced Cellular-Energy Availability and Non-adaptive Energy Expenditure. Front Behav Neurosci. 2018;12:78.

[17] Mortimer JE, Waliany S, Dieli-Conwright CM et al. Objective physical and mental markers of self-reported fatigue in women undergoing (neo)adjuvant chemotherapy for early-stage breast cancer. Cancer-Am Cancer Soc. 2017;123(10):1810-1816.

[18] Raudonis BM, Kelley IH, Rowe N, Ellis J. A Pilot Study of Proinflammatory Cytokines and Fatigue in Women With Breast Cancer During Chemotherapy. Cancer Nurs. 2017;40(4):323-331.

[19] Feng LR, Wolff BS, Lukkahatai N, Espina A, Saligan LN. Exploratory Investigation of Early Biomarkers for Chronic Fatigue in Prostate Cancer Patients Following Radiation Therapy. Cancer Nurs. 2017;40(3):184-193.

[20] Ter Veer E, Prinsen H, Sprangers M et al. Interferon Gamma-Induced Protein (IP-10) as Potential Biomarker for Cancer-Related-Fatigue: Results from a 6-month Randomized Controlled Trial. Cancer Invest. 2018;36(7):371-377.

[21] Himbert C, Ose J, Lin T et al. Inflammation- and angiogenesis-related biomarkers are correlated with cancer-related fatigue in colorectal cancer patients: Results from the ColoCare Study. Eur J Cancer Care (Engl). 2019;28(4):e13055.

[22] Fossa A, Smeland KH, Fluge O et al. Metabolic analysis of amino acids and vitamin B6 pathways in lymphoma survivors with cancer related chronic fatigue. Plos One. 2020;15(1):e0227384.

[23] Verhaak E, Schimmel W, Sitskoorn MM et al. Multidimensional assessment of fatigue in patients with brain metastases before and after Gamma Knife radiosurgery. J Neurooncol. 2019;144(2):377-384.

[24] Ferris MJ, Zhong J, Switchenko JM et al. Brainstem dose is associated with patient-reported acute fatigue in head and neck cancer radiation therapy. Radiother Oncol. 2018;126(1):100-106.

[25] Pani F, Massidda M, Pusceddu V et al. Regorafenib-induced hypothyroidism and cancer-related fatigue: is there a potential link? Eur J Endocrinol. 2017;177(1):85-92.

[26] Mao H, Bao T, Shen X et al. Prevalence and risk factors for fatigue among breast cancer survivors on aromatase inhibitors. Eur J Cancer. 2018;101:47-54.

[27] Repka CP, Hayward R. Effects of an Exercise Intervention on Cancer-Related Fatigue and Its Relationship to Markers of Oxidative Stress. Integr Cancer Ther. 2018;17(2):503-510.

[28] Grossberg AJ, Vichaya EG, Christian DL et al. Tumor-Associated Fatigue in Cancer Patients Develops Independently of IL1 Signaling. Cancer Res. 2018;78(3):695-705.

[29] Lai S. Cancer related fatigue and cancer cachexia are the consequence of endocrine failure caused by persistent stress. Med Hypotheses. 2019;123:60-62.

[30] Weber D, O'Brien K. Cancer and Cancer-Related Fatigue and the Interrelationships With Depression, Stress, and Inflammation. J Evid Based Complementary Altern Med. 2017;22(3):502-512.

[31] Xiao C, Miller AH, Felger J et al. Depressive symptoms and inflammation are independent risk factors of fatigue in breast cancer survivors. Psychol Med. 2017;47(10):1733-1743.

[32] Peoples AR, Roscoe JA, Block RC et al. Nausea and disturbed sleep as predictors of cancer-related fatigue in breast cancer patients: a multicenter NCORP study. Support Care Cancer. 2017;25(4):1271-1278.

ISSN: 2710-0588 DOI: 10.29556/FSE.202109_1(6).0022

[33] Chao HH, Doucette A, Raizen DM, Vapiwala N. Factors associated with fatigue in prostate cancer (PC) patients undergoing external beam radiation therapy (EBRT). Pract Radiat Oncol. 2018;8(3):e139-e148.

[34] Esser P, Gotze H, Mehnert-Theuerkauf A, Knoop H, Kuba K. Fear of progression and its role in the relationship of cancer-related fatigue with physical functioning and global quality of life - A register-based study among hematological cancer survivors. J Psychosom Res. 2019;127:109844.

[35] Xiao C, Beitler JJ, Higgins KA et al. Associations among human papillomavirus, inflammation, and fatigue in patients with head and neck cancer. Cancer-Am Cancer Soc. 2018;124(15):3163-3170

[36] Liao M, Xie Y, Yan J et al. Effect of acupuncture at 3 anti-fatigue acupoints in the treatment of cancer-related fatigue in patients with cancer: Protocol for a systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019;98(23):e15919.

[37] He L, Xu D, Jia C et al. Effect of Fatigue Three-Needle acupuncture therapy in a patient with cancer-related fatigue: A case report. Medicine (Baltimore). 2019;98(20):e15659.

[38] Huang Z, Zhang Q, Fan Y et al. Effect of Traditional Chinese Medicine Injection on Cancer-Related Fatigue: A Meta-Analysis Based on Existing Evidence. Evid Based Complement Alternat Med. 2020;2020:2456873.

[39] Cheng CS, Chen LY, Ning ZY et al. Acupuncture for cancer-related fatigue in lung cancer patients: a randomized, double blind, placebo-controlled pilot trial. Support Care Cancer. 2017;25(12):3807-3814.

[40] Khanghah AG, Rizi MS, Nabi BN, Adib M, Leili E. Effects of Acupressure on Fatigue in Patients with Cancer Who Underwent Chemotherapy. J Acupunct Meridian Stud. 2019;12(4):103-110.

[41] Zhu G, Zhang B, Jiang F, Zhao L, Liu F. ShenQi FuZheng Injection ameliorates fatigue-like behavior in mouse models of cancer-related fatigue. Biomed Pharmacother. 2019;111:1376-1382.

[42] Yennurajalingam S, Tannir NM, Williams JL et al. A Double-Blind, Randomized, Placebo-Controlled Trial of Panax Ginseng for Cancer-Related Fatigue in Patients With Advanced Cancer. J Natl Compr Canc Netw. 2017;15(9):1111-1120.

[43] Xu Y, Wang XS, Chen Y et al. A Phase II Randomized Controlled Trial of Renshen Yangrong Tang Herbal Extract Granules for Fatigue Reduction in Cancer Survivors. J Pain Symptom Manage. 2020;59(5):966-973.

[44] Zhang Y, Li Z, Zhao Z et al. Effect of the Chinese Medicine YangZheng XiaoJi on Reducing Fatigue in Mice with Orthotopic Transplantation of Colon Cancer. Evid Based Complement Alternat Med. 2019;2019:3870812.

[45] Song S, Yu J, Ruan Y et al. Ameliorative effects of Tai Chi on cancer-related fatigue: a meta-analysis of randomized controlled trials. Support Care Cancer. 2018;26(7):2091-2102.

[46] Lu Y, Qu HQ, Chen FY et al. Effect of Baduanjin Qigong Exercise on Cancer-Related Fatigue in Patients with Colorectal Cancer Undergoing Chemotherapy: A Randomized Controlled Trial. Oncol Res Treat. 2019;42(9):431-439.

[47] Zhou YT, Li SS, Ai M et al. 1,25(OH)2D3 mitigate cancer-related fatigue in tumor-bearing mice: Integrating network pharmacological analysis. Biomed Pharmacother. 2020;128:110256.

[48] Shindo T, Kobayashi K, Tanaka T, Masumori N. Can levocarnitine supplementation improve fatigue caused by sunitinib as a treatment for renal cell carcinoma? A single-center prospective pilot study. Support Care Cancer. 2019;27(4):1491-1496.

[49] Endo K, Ueno T, Ishikawa K et al. Effects of l-carnitine administration on health-related quality of life during cisplatin-based chemoradiotherapy in patients with head and neck squamous cell carcinoma. Auris Nasus Larynx. 2019;46(3):431-436.

[50] Marx W, Teleni L, Opie RS et al. Efficacy and Effectiveness of Carnitine Supplementation for Cancer-Related Fatigue: A Systematic Literature Review and Meta-Analysis. Nutrients. 2017;9(11).

[51] Wang XS, Shi Q, Mendoza T et al. Minocycline Reduces Chemoradiation-Related Symptom Burden in Patients with Non-Small Cell Lung Cancer: A Phase 2 Randomized Trial. Int J Radiat Oncol Biol Phys. 2020;106(1):100-107.

ISSN: 2710-0588 DOI: 10.29556/FSE.202109_1(6).0022

[52] Fukuoka S, Shitara K, Noguchi M et al. Prophylactic Use of Oral Dexamethasone to Alleviate Fatigue During Regorafenib Treatment for Patients With Metastatic Colorectal Cancer. Clin Colorectal Cancer. 2017;16(2):e39-e44.

[53] Kanbayashi Y, Hosokawa T. Predictors of the Usefulness of Corticosteroids for Cancer-Related Fatigue in End-of-Life Patients. Clin Drug Investig. 2017;37(4):387-392.

[54] Kroz M, Reif M, Glinz A et al. Impact of a combined multimodal-aerobic and multimodal intervention compared to standard aerobic treatment in breast cancer survivors with chronic cancer-related fatigue - results of a three-armed pragmatic trial in a comprehensive cohort design. Bmc Cancer. 2017;17(1):166.

[55] Poier D, Bussing A, Rodrigues RD et al. Influence of a Multimodal and Multimodal-Aerobic Therapy Concept on Health-Related Quality of Life in Breast Cancer Survivors. Integr Cancer Ther. 2019;18:1534735418820447.

[56] Van Dijk-Lokkart EM, Steur L, Braam KI et al. Longitudinal development of cancer-related fatigue and physical activity in childhood cancer patients. Pediatr Blood Cancer. 2019;66(12):e27949.

[57] Lam K, Li W, Chung OK et al. An integrated experiential training programme with coaching to promote physical activity, and reduce fatigue among children with cancer: A randomised controlled trial. Patient Educ Couns. 2018;101(11):1947-1956.

[58] Li W, Ho KY, Lam K et al. Adventure-based training to promote physical activity and reduce fatigue among childhood cancer survivors: A randomized controlled trial. Int J Nurs Stud. 2018;83:65-74.

[59] Adams SC, DeLorey DS, Davenport MH et al. Effects of high-intensity interval training on fatigue and quality of life in testicular cancer survivors. Br J Cancer. 2018;118(10):1313-1321.

[60] Mijwel S, Backman M, Bolam KA et al. Adding high-intensity interval training to conventional training modalities: optimizing health-related outcomes during chemotherapy for breast cancer: the OptiTrain randomized controlled trial. Breast Cancer Res Treat. 2018;168(1):79-93.

[61] Zhang Q, Li F, Zhang H, Yu X, Cong Y. Effects of nurse-led home-based exercise & cognitive behavioral therapy on reducing cancer-related fatigue in patients with ovarian cancer during and after chemotherapy: A randomized controlled trial. Int J Nurs Stud. 2018;78:52-60.

[62] Singh F, Galvao DA, Newton RU et al. Feasibility and Preliminary Efficacy of a 10-Week Resistance and Aerobic Exercise Intervention During Neoadjuvant Chemoradiation Treatment in Rectal Cancer Patients. Integr Cancer Ther. 2018;17(3):952-959.

[63] Zhou ES, Hall KT, Michaud AL et al. Open-label placebo reduces fatigue in cancer survivors: a randomized trial. Support Care Cancer. 2019;27(6):2179-2187.

[64] Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR. Open-Label Placebo Treatment for Cancer-Related Fatigue: A Randomized-Controlled Clinical Trial. Sci Rep. 2018;8(1):2784.

[65] Johnson JA, Garland SN, Carlson LE et al. Bright light therapy improves cancer-related fatigue in cancer survivors: a randomized controlled trial. J Cancer Surviv. 2018;12(2):206-215.

[66] Wu LM, Amidi A, Valdimarsdottir H et al. The Effect of Systematic Light Exposure on Sleep in a Mixed Group of Fatigued Cancer Survivors. J Clin Sleep Med. 2018;14(1):31-39.

[67] Lin PJ, Kleckner IR, Loh KP et al. Influence of Yoga on Cancer-Related Fatigue and on Mediational Relationships Between Changes in Sleep and Cancer-Related Fatigue: A Nationwide, Multicenter Randomized Controlled Trial of Yoga in Cancer Survivors. Integr Cancer Ther. 2019; 18:1534735419855134.

[68] Cramer H, Lauche R, Klose P et al. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. Cochrane Database Syst Rev. 2017; 1:CD010802.

[69] Zick SM, Colacino J, Cornellier M et al. Fatigue reduction diet in breast cancer survivors: a pilot randomized clinical trial. Breast Cancer Res Treat. 2017; 161(2):299-310.